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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,048	08/04/2003	Jallal Messadek	31927-CIP2	6961

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/635,048	MESSADEK, JALLAL	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27-42* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 31-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-25 and 27-30 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks filed on 22 February 2008 have been acknowledged and duly made of record.

Accordingly, the declaration as filed by Dr. Grandfils on 19 July 2007 has been duly acknowledged and made of record.

The essence of applicants' arguments is drawn to the properness of the references as cited in the current 103(a) rejection. Applicants' aver that the references separately and/or combined do not arrive at the claimed inventive objective of the claimed invention.

Specifically, applicants argue demotivation of the Cubicciotti reference based on alleged unrelatedness in the embodiments of controlled release systems electronically operated via chips and or other related devices to by which titration of a drug is achieved. Applicants' purport that based on the chemical properties, characteristics, and susceptibilities of glycine betaine, one of skill would not recognize the reasonable expectation of success via the incorporating a glycine betaine formulation in any of the devices as described by Cubicciotti et al.

Further, applicants aver the properness of Malamud based on the absence in said reference of the emphatic and direct mention of the incorporation of glycine betaine in the remote controlled drug delivery system.

Additionally, Murphy is addressed by applicant as alleged not teaching a direct glycine betaine compound (consisting of).

The declaration as filed by Dr. Grandfils further elucidates the alleged deficiencies of the references as mentioned *supra*. Essentially, the declaration discloses that references Malamud and Murphy teach non-analogous art with regard to the limitation drawn to the administration of

a formulation consisting exclusively of glycine betaine (with accompanying additives). Dr. Grandfils avers the lack of reasonable modification of the representative device and system embodiments of Cubicciotti in view of the chemical make-up of the glycine betaine compound.

Applicants' arguments are considered but are not found persuasive.

Thus, rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant invention.

Claim Rejections - 35 USC § 103 (New Matter Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 14-25, 27-30 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ushiyama et al. (USPN 4,605,548) and D'Angelo et al. (USPN 5,405,614) (D'Angelo '614, hereinafter) in view of Mitragotri et al. (USPN 5,814,599) and Cleary (USPN 4,911,916) and Malamud et al (USPN 5, 928, 195).

Principally, in consideration of the inventive objective of applicants' claimed invention, the limitations of particularly claims 14 and 17 are related but may also be interpreted as distinct in view of the broadness of claim 14. Claim 17 is drawn to a more mechanized delivery system. Claim 14 is drawn to a conventional transdermal delivery system incorporated with variable matrices which release drug components over a more sustained period of time. Each system, whether conventional or mechanized may also exhibit similar intervals of release of active component in correspondence with the minute limitations drawn to the claims.

In view of the above, Ushiyama et al. teach a drug admin. material for continuously administering an active drug at a controlled rate through an integument comprises an adhesive film which comprises a film and a pressure sensitive layer, a barrier layer, a drug-retaining layer, a drug admin. layer which continuously feeds an active drug to the integument and a delaminatible protective film, the drug admin. layer comprising a porous membrane contg.in pores a liq. having a limited solubility for the active drug, so that the liq. is stably retained in the porous membrane by capillary pressure (abstract only).

Ushiyama et al. teach [an] [...] invention [which] provides a drug administration material for administering a drug continuously and constantly, which enables administration of an active drug released from a drug-retaining layer of the drug administration material through integument or mucous membrane using a drug administration layer comprising a novel porous membrane

whose pores are filled with a liquid having a limited solubility for the drug (col. 1, l/s 64-68; column 2, l/s 1-3)

More particularly, the present invention provides a drug administration material useful for administering an active drug continuously at a constant rate through integument or mucous membrane, which comprises a drug-retaining layer having provided on at least one side thereof an administration layer capable of supplying an active drug continuously to integument or to mucous membrane, said administration layer comprising a porous membrane and a liquid which is filled in the pores of the membrane and has a limited solubility for the drug (cols. 1 and 2, l/s. 64-68 and 1-14, respectively).

Specifically, the drug administration material of the present invention is significant in that the liquid contained in the drug administration layer is designed so that the liquid dissolves a drug coming into contact with the drug administration layer to feed the drug to integument or to mucous membrane. The liquid continues to dissolve the drug up to saturation, and after saturation stops dissolving the drug. **When the drug administration material of the present invention is brought into contact with integument or mucous membrane and absorbed there through, the drug level in the liquid decreases from saturation. Then, the liquid again starts dissolving the drug, and while the material is applied to integument or to mucous membrane, the liquid continues to dissolve the drug until the drug is substantially exhausted from the drug-retaining layer. Thus the active drug is applied to integument or mucous membrane continuously at a constant rate** (col. 5, l/s. 51-68).

Thus, based on the above explanation, the limitations in the instant claims drawn to ranges in intervals of continuous and sustained administration of a bioactive substance (e.g. glycine betaine) are readily encompassed by the teachings of Ushiyama et al. Claim 42 discloses said system **being adapted** for releasing in a time-controlled manner for at least 2160 minutes. The conversion in regard to more familial measures in view of pharmaceutical administration would be 36 hours. Thus, one of skill would be inclined to recognize a conventional transdermal system as being fully capable of providing such sustained administration of any drug of choice if adapted appropriately.

Ushiyama et al. does not teach the incorporation of electronic devices and chips drawn to a transdermal drug delivery system.

However, D'Angelo et al. teach embodiments replete with descriptions and explanations drawn to electronically/ electrically- based transdermal drug delivery systems:

a base unit having a timer and electrical connections for issuing electronic timing information from said timer; a drug administration unit electrically connected to said base unit, said drug administration unit having a housing defining a space therein for receiving a drug and said housing having drug dispensing conduit means formed therein, a skin-contacting surface to be placed on a patient's skin, dispensing means for selectively causing time-dependent dispensing of a drug from said space in said housing through said conduit means to said skin-contacting surface and to the patient's skin, and means for generating pressure waves at said skin contacting surface for facilitating transdermal absorption of the drug dispensed to said skin contacting surface (col. 13, l/s 16-33).

D' Angelo '614 does not teach the incorporation of glycine betaine emphatically. Further, D'Angelo '614 does not provide reasoning as to why it would be pharmaceutically advantageous to incorporate glycine betaine based on its properties into a transdermal drug delivery system.

However, the deficiencies in D'Angelo '614 are resolved by the teachings of Mitragotri et al. which teach hydrophilic molecules generally due to their quality of enhanced transdermal penetration (col. 5, l/s 18-22; col. 13, l/s. 10-12).

Mitragotri et al. does not teach glycine betaine directly or expressly but provides reasoning as to the benefits of hydrophilic compounds in pharmaceutical formulations for transdermal delivery.

In view of the teachings of Mitragotri et al., Cleary discloses reasoning drawn to the well-known of compound/drug compatibility studies. As disclosed, the compound glycine betaine is hydrophilic and highly soluble in water. Thus, Cleary disclose embodiments drawn principally to a drug reservoir for transdermal delivery devices comprising soln. of drug in hydrophobic polymer embedded in pores of polymer foam (col. 2, l/s. 18-68). Hydrophobic polymeric porous compartments, walls, coverings, layers, etc are indicated in association with drugs that require increased permeability into the skin. The Mitragotri reference directly above explains that due the hydrophilic nature of a drug (e.g. glycine betaine), that permeation into the skin would be more readily facilitated. The Cleary reference offers reasoning as to why such a hydrophilic drug (as would be apparent to one of skill) would be further facilitated via covering or compartmentalization with a hydrophobic polymer in order to preserve the integrity of the glycine betaine compound for effective administration.

All references above do not teach glycine betaine.

However, Malamud et al. teach compounds containing a betaine compound (note the term *betaine* is interchangeable with the term glycine betaine) (col.5, l. 38) .

The common teaching, despite the absence of any mention of glycine betaine as a compound unit, the resultant effect of facilitated permeability of the skin is noted via such combinations. Please refer to Mitragotri et al. and D'Angelo et al. above.

Absent of any explanation in the specification drawn explicitly to a transdermal drug delivery device (with an electronic device/chip) administering glycine betaine, the one of skill would reasonably see that such devices are indicated for a myriad of bioactive substances including those with the properties, characteristics and susceptibilities of glycine betaine.

Absent of any explanation in the specification as to actual embodiments drawn to a transdermal delivery system incorporating electronical devices and chips for the administration of glycine betaine, one of skill would instantly recognize the variable susceptibilities of glycine betaine and the obvious need for compatible storage for administration for such a compound.

Thus, it would be prima facie obvious to one of skill in the art at the time of invention to at once recognize a reasonable expectation of success via the combining together of Ushiyama, D'Angelo et al., Mitragotri et al. , Cleary, and Malamud.

Ushiyama essentially teach the inventive objective disclosed in all claims of the claim set with the exception of those claims drawn specifically to an electronic device and/or chip. D'Angelo et al. teach the limitations of those claims drawn specifically to transdermal delivery devices incorporating electronic/electrical circuitry. It is known in the art by one of skill that the

same therapeutic goal of the release of a time-controlled formulation for at least 2160 minutes could be achieved with a conventional transdermal drug delivery system as well as a mechanized transdermal drug delivery system. Mitragotri et al. teach drug compatibility properties with reference to hydrophilic compounds (in the absence of any mention of glycine betaine). However, as adequately disclosed, glycine betaine is hydrophilic. Thus, increased permeability as an osmotic solute and/or osmo-protectant is also well-recognized in the art. The motivation to combine Cleary with the above is drawn to its disclosure with references to hydrophobic compartmentalized/contained units which are in contact with drug agents or house drug agents. It would be obvious to one of skill that a molecule or a mixture thereof of glycine betaine would be adequately contained in a hydrophobic environment as opposed to a hydrophilic environment. This, in effect, would preserve the integrity of the therapeutic efficacy of said glycine betaine. Lastly, Malamud as referenced earlier, contains mixtures containing both glycine and betaine, respectively. However, the same effect is observed with these mixtures as would be observed with glycine betaine.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB